Low and High Birth Weight and the Risk of Child Attention Problems

Nina H. van Mil, MSc[1,2,3], Régine P. M. Steegers-Theunissen, MD, PhD[3], Ehsan Motazedi, MSc[4], Pauline W. Jansen, PhD[1,2], Vincent W. V. Jaddoe, MD, PhD[1,5,6], Eric A. P. Steegers, MD, PhD[3], Frank C. Verhulst, MD, PhD[2], and Henning Tiemeier, MD, PhD[2,5,7]

Objective To study the prospective association between birth weight and attention problems and to explore the role of maternal body mass index (BMI) in this association.

Study design In 6015 children of a population-based cohort (Rotterdam, The Netherlands, 2001-2005), information on birth weight was collected and gestational age-adjusted SDS were calculated. At age 6 years, parents assessed attention problems with the Child Behavior Checklist. We used linear regression to study the association of birth weight with attention problem score and examined the modification of this association by maternal early pregnancy BMI.

Results The observed association between birth weight and attention problem score was curvilinear (adjusted β per birth weight SDS^2: 0.02, 95% CI 0.00; 0.03, P = .008); the turning point equals 3.6 kg at term. In analyses of the extreme tails of the birth weight distribution, the associations with attention problem score disappeared after adjustment for socioeconomic confounders. Maternal early pregnancy BMI moderated the association of child birth weight with attention problem score (P interaction = .007, with curvilinear term in model).

Conclusions Higher birth weight was related to less attention problems but from a birth weight of about 3.6 kg or more, a higher birth weight did not reduce the risk of attention problems any further. However, in children of obese mothers (BMI >30 kg/m^2), high birth weight may increase the risk of attention problems. *(J Pediatr 2015;166:862-9)*.

Low birth weight has been linked to depression, anxiety,[1] and schizophrenia,[2,3] and in particular to childhood attention deficit hyperactivity disorder (ADHD).[4] Children with low birth weight are at a greater risk of symptoms of inattention and to a lesser extend at risk of hyperactivity/impulsivity.[5,6]

A full understanding of the association between birth weight and ADHD symptoms has been hampered by several limitations. First, with a few exceptions, previous studies have focused on the lower end of the birth weight distribution. Children with a very low birth weight (<1.5 kg) or moderately low birth weight (<2.5 kg) were repeatedly reported to have an increased risk of ADHD symptoms.[4] Some studies have suggested nonlinear associations between birth weight and cognitive and behavioral functioning,[7,8] but a relation between the entire range of birth weight and ADHD symptoms is not well established. Studies that modeled birth weight as a continuous exposure include investigations of Linnet et al, Schlotz et al, Hultman et al, and Kelly et al.[9-12] Whereas these studies observed an inverse relationship between birth weight and risk of ADHD symptoms or ADHD diagnosis, Lahti et al[13] did not observe an association.

Second, since these studies were conducted, the population distribution of birth weight has changed. Over the last decades, a rise in median birth weight was observed.[14] It has been suggested that the increase in birth weight is explained by, among other factors, higher maternal body mass index (BMI) and altered smoking patterns.[15] However, studies have not investigated the association between the continuum of child birth weight and ADHD symptoms in children born in the last 2 decades.

We postulated that because of time trends in mother's weight the relationship between child birth weight and attention problems may have changed. In a large population-based cohort, we addressed the following aims. First, we investigated the linear association between birth weight and Child Behavior Checklist (CBCL/1.5-5) attention problem score at age 6 years and also determined if the association between birth weight and attention problem score at age 6 years is curvilinear. In addition to this aim, we studied the associations between low and high birth weight with attention problem score. We also examined the role of maternal early pregnancy BMI in these associations. We tested whether maternal early pregnancy BMI precedes high child birth weight and accounts for its association with ADHD using a mediation analyses. In addition, we tested whether the association between child birth weight and attention

ADHD	Attention deficit hyperactivity disorder
BMI	Body mass index
CBCL	Child Behavior Checklist

From the [1]The Generation R Study Group and Departments of [2]Child and Adolescent Psychiatry/Psychology, [3]Obstetrics and Gynecology, [4]Biostatistics, [5]Epidemiology, [6]Pediatrics, and [7]Psychiatry, Erasmus Medical Center, Rotterdam, The Netherlands

The Generation R Study was supported by Erasmus Medical Center, Erasmus University Rotterdam, The Netherlands Organization for Health Research and Development (ZonMw) 'Geestkracht' program (10.000.1003), The Netherlands Organisation for Scientific Research, the Ministry of Health, Welfare and Sport, and the Ministry of Youth and Families. N.M. was supported by the Sophia Foundation for Medical Research (268). F.V. is publisher of the Dutch translations of Achenbach System of Empirically Based Assessment from which he receives remuneration. The other authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2014.12.075

problems is moderated by maternal early pregnancy BMI by using an interaction model. We hypothesized that low and very high birth weights confer a higher risk of attention problems than average birth weight. No hypothesis for the effect of maternal early pregnancy BMI on this association was formulated.

Methods

This analysis was embedded in the Generation R Study, an ongoing population-based birth cohort from fetal life onward.[16] All pregnant women were enrolled between 2001 and 2005 in Rotterdam, The Netherlands. Assessments during pregnancy and childhood comprised physical examinations, ultrasonography, biological sampling, and parental questionnaires. The study was approved by the Medical Ethical Committee of the Erasmus Medical Center in Rotterdam. Written consent was obtained from all participating women.

In total, 8301 mother-child pairs participated in the postnatal phase of the Generation R study. As depicted in the flow chart of the study population (**Figure 1**; available at www.jpeds.com) of 8009 mothers who gave birth to singleton live-born children, information on child weight and gestational age at birth was available. Twin pregnancies (n = 200) were excluded because growth potentials for individual fetuses in multiple pregnancies are not comparable with singleton pregnancies. Parents of 6015 children (75%) provided behavioral data of the child at age 6 years by completing the CBCL/1.5-5. In 5448 mother-child pairs, information on birth weight, maternal early pregnancy BMI, and attention problem score was available.

To estimate gestational age, crown-rump length (until a gestational age of 12 weeks and 5 days), or biparietal diameter (from 12 weeks and 5 days onward), measured by fetal ultrasound examination, as previously described,[17] were used. Inter- and intraobserver intraclass correlation coefficients were all >0.98.[17] Information on birth weight of the child was obtained from community midwifery and hospital registries. Birth weight was established directly postpartum and expressed in kilograms (kg).

To disentangle the effects of birth weight from gestational age, we express birth weight in units adjusted for gestational age and sex (ie, birth weight SDS). The birth weight SDS were constructed based on distributions in the Generation R cohort.[18]

We measured attention problem score of the child at 6 (range 4.9-8.0) years of age by using the attention problems subscale of the CBCL/1.5-5. The CBCL is a parent-report questionnaire that contains 99 problem items rated on a 3-point scale: 0 (not true), 1 (somewhat or sometimes true), and 2 (very true or often true). By summing the raw scores, seven syndrome scales, including the continuous attention problems scale, consisting of 5 items, can be computed (Cronbach alpha 0.70). Higher scores represent higher severity of problems. For the CBCL good reliability and validity have been reported.[19]

Maternal Anthropometrics

In early pregnancy (median gestational age 14.4 weeks, IQR 12.5-17.8), maternal height and weight were measured without shoes and heavy clothing. BMI (kg/m^2) was calculated using weight (kg) and height (cm) in 5448 women. Throughout the article, we refer to this variable as 'early pregnancy BMI'. The correlation between early pregnancy BMI and prepregnancy BMI (n = 4619) obtained by questionnaire in early pregnancy was very good (Pearson correlation 0.95 [$P < .001$]).

Covariates

Possible confounders of the association between birth weight and attention problem score were derived from the literature.[20,21] Child sex, Apgar score, mode of delivery, presence of gestational diabetes, and pre-eclampsia were derived from medical records completed by midwives and gynecologists. At enrollment (median gestational age 14.7 weeks, SD 3.6) we obtained information on maternal age, national origin, educational level, parity, prenatal smoking, alcohol use, and folic acid supplementation by questionnaire. National origin of the mother was based on the country of birth of the parents. Educational level of the pregnant woman was assessed by the highest completed education and categorized as primary school only, secondary school, or higher education. Maternal prenatal smoking and alcohol use were classified as 'no use,' 'use until pregnancy was confirmed,' and 'continued use during pregnancy.' Folic acid supplementation was classified as 'no use,' 'use started during the first 10 weeks of pregnancy,' or 'use started preconceptional.' At 20 weeks pregnancy, we measured maternal psychological symptoms using the Brief Symptom Inventory.[22] In this study, the total sum scale of maternal psychological symptoms was tested as a confounder, as maternal psychopathology may affect both fetal growth and may independently be related to child behavioral problems. Moreover, as this study is based on parent report information on attention problems, maternal psychological symptoms may influence the report. All analyses were also adjusted for age at attention problem assessment.

Statistical Analyses

Attention problems were studied as a continuous outcome using linear regression models. To approximate a normal distribution, the CBCL attention problem scale is square-root transformed. In the first step of our analyses, we studied whether birth weight of the child was linearly related to attention problem score at age 6 years in our population. Second, we explored a curvilinear association with attention problem score by adding a squared term of birth weight to the model. Third, we investigated low birth weight (as defined by <10th and <20th percentile SDS) and high birth weight (as defined by >90th and >80th percentile SDS) in relation to attention problems. We report the results of the 10% and 20% extremes on both ends of the birth weight distribution to test whether results depended on any choice of cut-off. We defined low and high birth weight based on population-